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Case of the Month

Acromegaly and its treatment in the McCune–Albright syndrome

L. D. K. E. Premawardhana, J. P. Vora, R. Mills* and M. F. Scanlon

*Departments of Medicine and *Surgery, University of Wales College of Medicine, Cardiff, UK*

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Summary

The McCune–Albright syndrome, comprising polyostotic fibrous dysplasia, cutaneous pigmentation and endocrine hyperfunction, is occasionally complicated by acromegaly due to a pituitary adenoma. We report a patient with the McCune–Albright syndrome and acromegaly, who developed secondary hypothyroidism and hypoadrenalism, in whom surgical removal of the pituitary tumour was technically difficult. A combination of a long-acting somatostatin analogue ('Sandostatin') and external irradiation were therefore used as treatment.

Over 50 years ago, McCune and Albright described a syndrome characterized by polyostotic fibrous dysplasia, cutaneous pigmentation and endocrine hyperfunction (McCune, 1936; Albright *et al.*, 1937). Sexual precocity, occurring more frequently in girls, is by far the most common endocrinopathy (Maurag & Blizzard, 1986). Since then, other endocrinopathies have been described in association with the syndrome, including hyperthyroidism, Cushing's syndrome, hyperprolactinaemia, hypophosphataemic rickets and acromegaly. We report a patient with the characteristic triad of the McCune–Albright syndrome who developed acromegaly due to a radiologically confirmed pituitary adenoma.

Case presentation

The patient, a 26-year-old Caucasian female, had left sided nasal obstruction and rhinorrhoea following a left partial maxillectomy under general anaesthesia for the McCune–Albright syndrome which was diagnosed following the onset of intermittent vaginal bleeding and breast enlargement at the age of 3 years. Patchy cutaneous pigmentation and fibrous dysplasia were observed in early childhood. Menarche was fully established at 8–9 years. During adolescence, shortening of the left femur due to dysplastic changes was treated by multiple osteotomies with bone grafting.

Correspondence: Dr L. D. K. E. Premawardhana, Division of Endocrinology, Department of Medicine (7th Floor), University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK.

Enquiry revealed enlargement of feet (shoe size (UK) increasing by $2\frac{1}{2}$) and increased sweating for 1 year approximately. There was no headache, visual disturbance, weight gain or galactorrhoea. Menses were regular. There was no relevant family history. The patient was married but had no children.

Examination revealed facial asymmetry with prominence of her left maxilla and mandible. Her skin was greasy and thickened. Areas of flat, irregular cutaneous pigmentation were present bilaterally but did not cross the midline (Fig. 1). However, other features of acromegaly such as acral enlargement, prognathism or prominence of supraorbital ridges, goitre or galactorrhoea were not observed. Visual fields and fundi were normal.

The results of endocrine evaluation were consistent with acromegaly with growth hormone (GH) levels during a day profile ranging between 16·0 and 37·7 mU/l. Glucose tolerance was normal (fasting and 2-hour values being 4·9 and 6·5 mmol/l respectively), but GH levels failed to suppress adequately from a basal value of 34·5 mU/l to a minimum of 14·8 mU/l. TRH produced a paradoxical rise in GH from 27·0 to over 100 mU/l. Basal prolactin (PRL) was 310 mU/l with a normal response to TRH. During insulin-induced hypoglycaemia (plasma glucose 1·8 mmol/l) GH rose from 35 to 52 mU/l and prolactin levels remained stable at approximately 400 mU/l. However, plasma cortisol levels were unrecordable (< 28 nmol/l) during the basal period and following administration of insulin. Other investigations revealed free T_4 9 pmol/l; TSH 1·5 mU/l; LH 5·4 U/l; FSH 3·5 U/l; 17-β-oestradiol 80 pmol/l and progesterone < 2 nmol/l.

High resolution CT scan of the pituitary fossa with contrast enhancement demonstrated an enhancing pituitary tumour with suprasellar extension with thickened surrounding bone and diffuse vault sclerosis clearly affecting occipital and parietal bones (Fig. 2).

Having confirmed the diagnosis of acromegaly due to a pituitary adenoma, she was started on hydrocortisone replacement therapy. Thereafter a transethmoidal hypophysectomy was undertaken. At operation the enlarged pituitary was surrounded by a 'venous lake' and surgical access was not possible due to haemorrhage. Surgery was therefore abandoned.

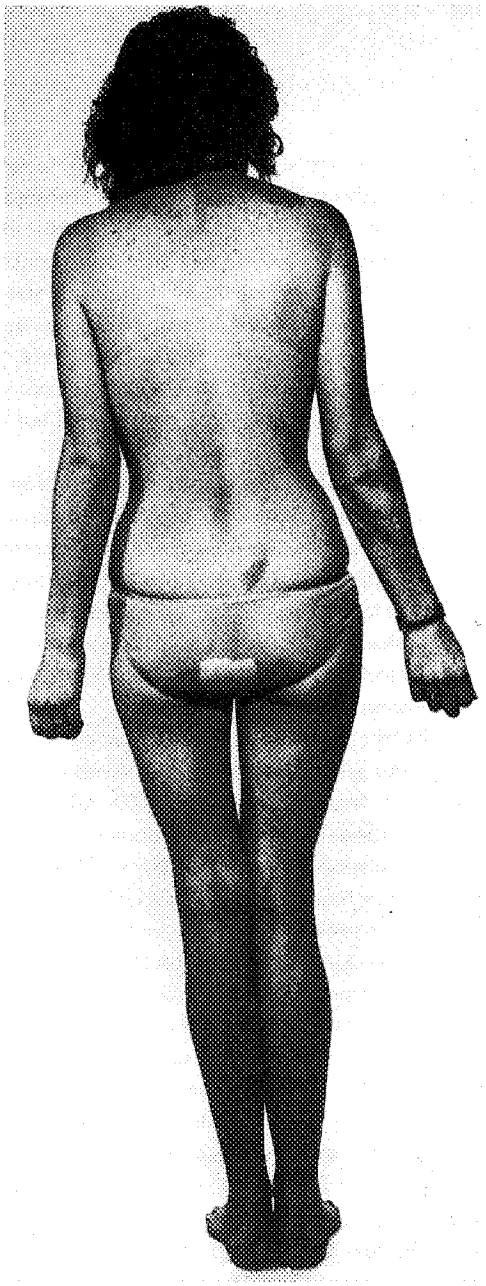

Fig. 1 Cutaneous pigmentation, with irregular margins in McCune–Albright syndrome. Shortening of the left femur is also visible.

Following attempted surgery, elevated GH levels were confirmed during a day profile and pituitary irradiation was undertaken by means of three-field external deep irradiation therapy. In the interim, GH hypersecretion was treated medically. A single dose of bromocriptine 2·5 mg orally, reduced growth hormone levels from 54·4 to 26·3 mU/l at 2 hours rising to 39·6 mU/l at 4 hours post administration. By contrast, 100 μg Sandostatin (octreotide, Sandoz) subcutaneously reduced GH levels from 58·8 to 7·1 mU/l at 2 hours and thereafter to 21·0 mU/l at 4 hours post injection.

Persistent secondary hypothyroidism (free T_4 10 pmol/l and TSH 1·2 mU/l) was thereafter treated with L-thyroxine 100 μg//day. She was commenced on treatment with octreotide 100 μg three times daily subcutaneously and hydrocortisone 10 mg twice daily.

An initial short lived watery diarrhoea settled and she has been free of side-effects. Clinical improvement was noticed by lack of excessive sweating and decrease in the size of her feet.

One year into treatment her GH day profiles showed partial suppression (9·8–13·6 mU/l) but remain high off treatment for a week (32–64 mU/l). CT scans did not show significant change in size of tumour or suprasellar extension. Her liver function tests, thyroid function tests, fasting and 2-hour postprandial blood sugars and HBA1C were completely normal. She was free of symptoms of gall bladder calculi. Her dose of octreotide has now been increased to 150 μg three times daily.

Discussion

Acromegaly is a rare endocrinopathy associated with the McCune–Albright syndrome. Reviews of the literature by Lipson and Hsu (1981) and Cuttler *et al.* (1989) revealed six and 17 cases respectively of well documented clinical and biochemical acromegaly. Our patient fulfilled the biochemical criteria of acromegaly: high daytime GH levels, non-suppression during oral glucose tolerance testing, and increase after TRH. The surprising endocrine findings in our patient were of marked hypoadrenalism (despite successfully undergoing a general anaesthetic prior to presentation), together with subsequent development of hypothyroidism. As far as we are aware this has not been reported in the McCune–Albright syndrome. GH hypersecretion in the McCune–Albright syndrome differs in several respects from that observed in classical acromegaly. Presentation of gigantism/acromegaly is considerably earlier than in classical acromegaly. In one review, 14 out of 17 patients were below 30 years of age (Lipson & Hsu, 1981). Less than half the patients with McCune–Albright syndrome and acromegaly show radiological evidence of a pituitary adenoma compared with 80–90% in classical acromegaly. Of Cuttler's series only three showed suprasellar extension as in our patient. Hyperprolactinaemia was not observed in our patient in contrast to 85% of patients with McCune–Albright syndrome combined with GH hypersecretion. By comparison, hyperprolactinaemia is a feature of 30–40% of patients with classical acromegaly.

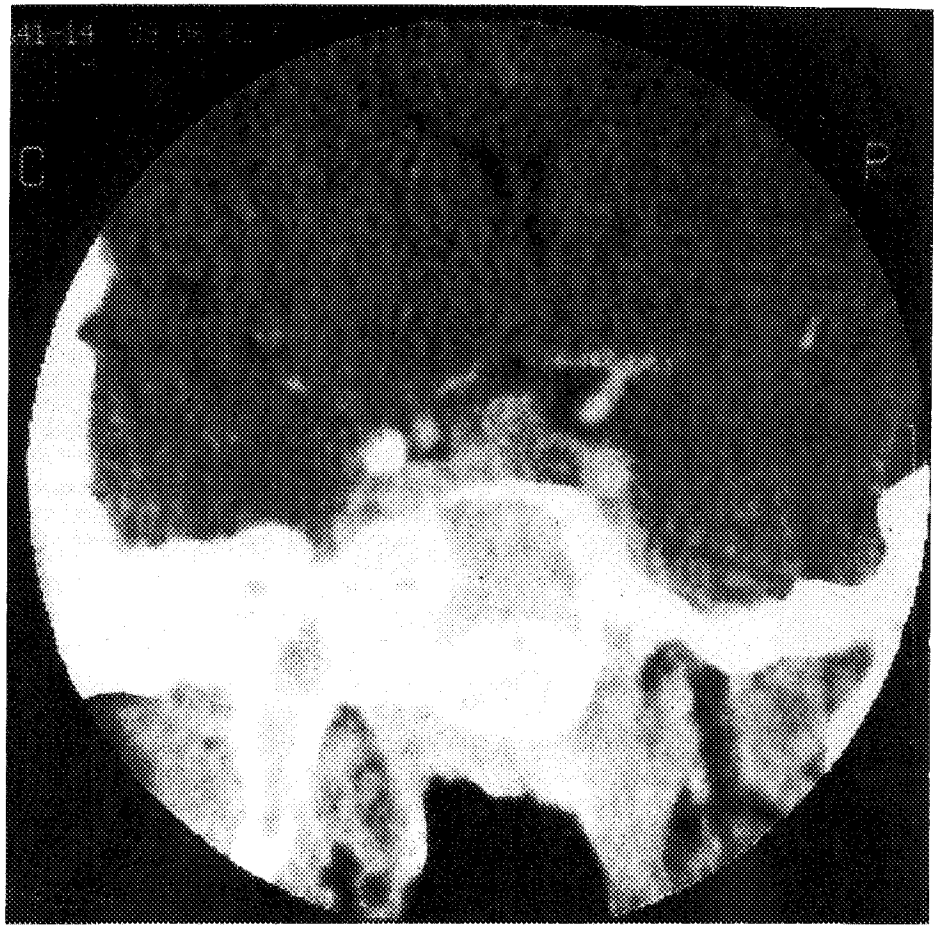

Fig. 2 High resolution contrast enhanced pituitary scan showing fibrous dysplasia of the left temporo-parietal-occipital bones, and pituitary tumour with suprasellar extension.

Pituitary surgery in this syndrome is beset with problems mainly related to fibrous dysplasia and the resultant thickening of bones. At surgery our patient proved to have abnormally thickened dysplastic maxillary and ethmoid bones. However, increased vascularity surrounding the pituitary gland prevented surgical intervention.

The ineffectiveness of bromocriptine in completely suppressing GH levels prompted the use of the long acting somatostatin analogue, octreotide (Sandostatin, Sandoz). Geffner *et al.* (1987) first reported the use of somatostatin in acromegaly associated with the McCune–Albright syndrome. Octreotide has a half-life of 110 minute after subcutaneous injection, and an overall duration of effect of about 6–8 hours (Barnard *et al.*, 1986). A single subcutaneous injection of octreotide produces a reduction of GH levels in 30–60 minutes and maximally suppresses GH levels between 2 and 4 hours. Levels may rise to preinjection levels 8 hours after injection (Frohman, 1991). Our patient's data are consistent with these findings. Although long-term suppressiveness can be predicted by the acute suppressive effects of a single injection—a reduction of 88% at 2 hours in our patient (Lamberts *et al.*, 1989)—the lack of complete suppression after a year of treatment may be due to an inadequate dose or reduced numbers of somatostatin receptors in the GH secreting adenoma of our patient. Ten to 30% of GH secreting tumours are known to have reduced somatostatin receptors (Reubi & Landolt, 1989). The effects of octreotide on tumour shrinkage are less predictable. Although both microadenomas and macroadenomas have been known to shrink, only about half of all GH secreting tumours decrease in size (Frohman, 1991). Our patient's tumour has not changed in size. We used radiotherapy in addition to octreotide to prevent tumour expansion, particularly in view of the suprasellar extension.

In conclusion, we suggest that the combination of a somatostatin analogue and radiotherapy may be the treat-

ment of choice in patients with McCune–Albright syndrome and acromegaly, in view of the technical difficulties associated with pituitary surgery in this syndrome.

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Commentary

Giovanni Faglia

Institute of Endocrine Sciences, University of Milan, Italy

The Case of the Month (Premawardhana *et al.*, 1992) reports on a patient with the McCune–Albright syndrome in whom endocrine hyperfunction was expressed as precocious puberty and acromegaly. Unusually, secondary hypoadrenocorticism and hypothyroidism were present probably due to pituitary insufficiency caused by a huge GH-secreting pituitary adenoma. As the patient could not be operated on, she was treated with octreotide (which caused serum GH to fall by about 80%) in combination with radiotherapy.

Recently, Weinstein *et al.* (1991) have demonstrated the presence of somatic activating mutations in the α-chain of the stimulatory G protein—identical to those previously shown in some functioning endocrine tumours (Landis *et al.*, 1989; Lyons *et al.*, 1990; Suarez *et al.*, 1991)—in several tissues of four patients with McCune–Albright syndrome. These mutations cause substitution of other aminoacids for Arg 201 of $G_s\alpha$ resulting in the constitutive activation of adenylyl cyclase. As all the diverse syndromes of endocrine hyperfunction described in the McCune–Albright syndrome involve cells that respond to stimulatory hormones *via* the activation of adenylyl cyclase system and the subsequent cAMP formation as second messenger, it is likely that these mutations are responsible for unstimulated hormone hypersecretion (Levine *et al.*, 1991).

The subset of acromegalic patients with mutated $G_s\alpha$ pituitary GH-secreting tumours respond particularly well to octreotide treatment (Spada *et al.*, 1990). In view of this, it is reasonable to assume that octreotide is the first choice therapy for acromegaly associated with the McCune–Albright syndrome, and it is tempting to speculate that this drug might also control other associated endocrine hyperfunctions, provided that the involved glands possess somatostatin receptors.

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